IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC, Plaintiffs, v. EAGLE PHARMACEUTICALS INC., Defendant.	)	C.A. No. 18-823-CFC
PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC, Plaintiffs, v. AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, et al., Defendant.	)	C.A. No. 18-2032-CFC

DEFENDANTS' PROPOSED FINDINGS OF FACT
REGARDING INVALIDITY AND UNENFORCEABILITY

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Defendants Eagle Pharmaceuticals Inc. ("Eagle") and Amneal EU, Limited, Amneal Pharmaceuticals of New York LLC, Amneal Biosciences LLC, and Amneal Pharmaceutical Pvt. Ltd. (collectively "Amneal") (Eagle and Amneal collectively "Defendants") respectfully submit their proposed Findings of Fact Regarding Invalidity and Unenforceability.

FINDINGS OF FACT

I. INTRODUCTION

1. This is a patent infringement action brought under the provisions of the Hatch-Waxman Act, 21 U.S.C. § 355, and the Patent Act, 35 U.S.C. § 271. (No. 18-823, D.I. 268 ¶ 1, No. 18-2032, D.I. 282, ¶ 1.)

2. The procedural posture of this matter is set forth in the Joint Pretrial Order. (E-SF 7–14, 16, 17–19, 22–24, 28–34, 37, 39, 40, 42–45; A-SF ¶¶ 14–18, 20–22, 27–38, 40, 41–45.)[1]

3. No party has contested that subject matter jurisdiction is vested in this Court pursuant to 28 U.S.C. §§ 1331 and 1338. (No. 18-823, D.I. 268 ¶ 4, No. 18-2032, D.I. 282, ¶ 4.)

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[1] "E-SF" shall refer to the stipulated facts filed in the matter against Eagle, (No. 18-823, D.I. 268 at Ex. 1), whereas "A-SF" shall refer to the stipulated facts filed in the matter against Amneal. (No. 18-2032, D.I. 282 at Ex. 1).

4. No party has contested personal jurisdiction or venue. (No. 18-823, D.I. 268 ¶ 4, No. 18-2032, D.I. 282, ¶ 4.)

II. WITNESSES

A. Defendants

5. At trial, testimony from the following witnesses associated with Defendants were presented on the following topics.

1. Deposition Testimony By Plaintiffs' Designation

6. **Ronald Aungst** is the Senior Director of Global Program Management at Albany Molecular Research, Inc. ("AMRI"), and testified as a corporate designee on behalf of Eagle as well as on behalf of non-parties AMRI, and OSO BioPharmaceuticals Manufacturing, LLC ("OSO") regarding the manufacture of Eagle's ANDA Product. (Aungst Tr. 149:25–51:1.)

2. Dr. Kinam Park

7. Dr. Kinam Park testified as an expert in pharmaceutics and chemical development. (Park Tr. 344:25–45:1.)

8. Dr. Park holds the title of the Showalter Distinguished Professor in Biomedical Engineering at Purdue University, where he has taught biomedical and pharmaceutical sciences for over three decades, and has extensive experience formulating peptides. (Park Tr. 343:13–44:21.)

3. Dr. Carmen Cross

9. Dr. Carmen Cross testified as an expert clinician specializing in emergency medicine and critical care. (Cross Tr. 493:25–94:2.)

10. Dr. Cross has been a practicing physician specializing in emergency medicine and trauma critical care for approximately four decades, serving as both an emergency room attending physician and the chairman of the Department of Emergency Medicine of Columbia Memorial Hospital. (Cross Tr. 492:5–93:14.)

11. Dr. Cross has extensive experience in the administration of vasopressin products in emergency settings. (Cross Tr. 493:15–24.)

4. Dr. Leonard P. Chyall

12. Dr. Leonard Chyall testified as an expert in analytical testing of pharmaceutical formulations and the evaluation of data for such testing. (Chyall Tr. 560:18–61:2.)

13. Dr. Chyall has over two decades of experience as an organic chemist and pharmaceutical formulations contractor, in which he assisted in the development of various chemical formulations and their analytical and stability testing. (Chyall Tr. 558:25–59:22.)

B. Plaintiffs

14. At trial, testimony from the following witnesses associated with Plaintiffs was presented on the following topics.

1. Deposition Testimony By Defendants' Designation

15. **Vinayagam Kannan** testified as a fact witness as a former employee of Par (Kannan Tr. 520:3–8), and as a named inventor of the Asserted Patents and their patent family members (*see* DTX-605, JTX-1, JTX-2, JTX-3.)

16. **Matthew Kenney** testified as a fact witness as an employee of Par (Kenney Tr. 546:17–21), and as a named inventor of the Asserted Patents and their patent family members (*see* DTX-605, JTX-1, JTX-2, JTX-3.)

17. **Carla English** testified as a corporate designee on behalf of Plaintiffs regarding the identity of any individuals who contributed to the April 2014 Original Vasostrict Label. (English Tr. 653:20–54:1.)

18. **Craig Kenesky** testified as a fact witness regarding his work as Par's patent prosecution attorney for the Asserted Patents and their patent family members. (Kenesky Tr. 660:23–61:16.)

19. **Sunil Vandse** testified as a fact witness as a former employee of Par, and as a named inventor of the Asserted Patents. (Vandse Tr. 677:18–78:2; JTX-2, JTX-3.) Among other matters, Mr. Vandse testified on pH stability studies of vasopressin formulations, including those described in declarations to the U.S. Patent and Trademark Office ("the Vandse Declarations") and Examples 9 and 10 of the Asserted Patents. (Vandse Tr. 677:18–78:2.)

20. **Suketu Sanghvi** is the Senior Vice President for Research and Development at Par, and testified as a fact witness as a named inventor of the Asserted Patents, and as a corporate designee on behalf of Plaintiffs regarding issues relating to obviousness and criticality. (Sanghvi Tr. 686:8–18; JTX-2, JTX-3.)

2. Dr. Lee Kirsch

21. Dr. Kirsch testified as an expert in pharmaceutics, and, in particular, peptide pharmaceutical formulations and peptide stability. (Kirsch Tr. 196:20–22.)

22. Dr. Kirsch is a professor emeritus at the University of Iowa in the College of Pharmacy, Pharmaceutics Division. (Kirsch Tr. 194:20–95:8.)

23. Dr. Kirsch did not have any experience with vasopressin prior to the present matter. (Kirsch Tr. 261:6–9.)

3. Dr. Zlatan Coralic

24. Dr. Coralic testified as an expert in the clinical use and administration of intravenous drug products, including vasopressin. (Coralic Tr. 125:9–12.)

25. Dr. Coralic is an emergency medicine clinical pharmacist employed by UCSF Medical Center. (Coralic Tr. 122:23–23:22.)

III. HISTORY OF VASOPRESSIN

26. Vasopressin products have been on the market for nearly a century, before the advent of the FDA's drug approval process in 1938. (Park Tr. 390:24–91:13, 391:14–18; *see* DTX-25.9–10.)

27. Because these products existed before the FDA approval process, the FDA permitted several unapproved vasopressin products from a number of different manufacturers to be marketed. (DTX-25.9–10; DTX-38.5, 7; DTX-178.1, DTX-246.1; DTX-249.1; Cross Tr. 494:7–19; Coralic Tr. 141:21–42:6.)

28. The United States Pharmacopeia ("USP") had a standard in place for unapproved vasopressin product attributes, which included a recommended pH range of 2.5–4.5. (Park Tr. 391:19–92:12, 392:13–15; DTX-135.3–4.)

29. Those of ordinary skill in the art as of the priority date would have understood that vasopressin products would have good stability over the pH range of 2.5–4.5. (Park Tr. 392:21–93:1, 393:14–24; Kirsch Tr. 813:9–12, ("**Q.** So was the stability of a product with a known range of 2.5 to 4.5 considered to be a problem in the prior art? **A.** No.").)

30. JHP Pharmaceuticals, LLC ("JHP"), a predecessor to Par, marketed one such unapproved vasopressin product called Pitressin. (Park Tr. 390:22–91:13, Cross Tr. 495:9–96:4; DTX-25.9–10; DTX-38.5, 7; DTX-178.1.)

31. Pitressin was formulated with 20 units/mL vasopressin, 0.5% chlorobutanol, acetic acid and water. (Park Tr. 394:4–12; DTX-178.1; DTX-25.20.)

32. The pH of Pitressin was adjusted to 3.6 during manufacture. (Park Tr. 394:16–95:3; Kirsch Tr. 824:21–25:1; PTX-145 at EAGLEVAS0014352; DTX-25.20.)

33. Vasopressin products, including Pitressin, were used for decades to increase blood pressure in hypotensive patients. (Cross Tr. 493:15–24, 494:7–23, 496:5–18; Coralic Tr. 142:7–15; DTX-25.9–10.)

34. On September 25, 2012, JHP submitted NDA No. 204485 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act seeking approval for a vasopressin product based on Pitressin, *i.e.*, identical to that product but for the removal of ingredient overages for vasopressin and chlorobutanol at the FDA's request. (E-SF 7; A-SF ¶ 14; DTX-25.9; Park Tr. 395:17–25.)

35. JHP did not perform any clinical trials in support of NDA No. 204485 (Cross Tr. 497:1–3; DTX-42.8), but instead supported the clinical section of the NDA with only literature evidence. (Cross Tr. 497:1–19; DTX-42.8–10.)

36. On February 20, 2014, Par Pharmaceutical Companies, Inc. acquired JHP, which subsequently changed its name to Par Sterile Products, LLC. (E-SF 8; A-SF ¶ 15; Park Tr. 390:22–23.)

37. On April 17, 2014, the FDA approved NDA No. 204485 under the trade name VASOSTRICT®, which the parties refer to as "Original Vasostrict." (E-SF 9, 14; A-SF ¶¶ 16–17.)

38. The label for Original Vasostrict stated that this product was "adjusted with acetic acid to pH 3.4–3.6." (E-SF 12; A-SF ¶ 18.)

39. The only substantive difference between the unapproved Pitressin product and the Original Vasostrict product is the removal of vasopressin and chlorobutanol overages (*i.e.*, "an amount of a drug substance in excess of the label claim"), at the request of the FDA. (D.I. 276 at 3; Park Tr. 394:13–15, 395:17–25, 396:11–17; DTX-26.3.)

40. Subsequently, Par filed a supplement to its NDA (204485/S-003) seeking approval for a new formulation of Vasostrict with a sodium acetate buffer and change in manufacturing pH—from 3.4–3.6 in Original Vasostrict to 3.8—which the parties refer to as "Reformulated Vasostrict" and which was approved on March 18, 2016. (E-SF 17, 19; A-SF ¶ 20, 22.)

41. Par stopped selling Original Vasostrict in favor of Reformulated Vasostrict. (Park Tr. 397:5–7; *see also* Coralic Tr. 142:16–43:16; Kannan Tr. 714:20–23; Kirsch Tr. 767:2–4.)

42–50. [INTENTIONALLY LEFT BLANK]

IV. THE ASSERTED PATENTS

A. Overview

51. U.S. Patent 9,744,209 ("the '209 Patent") was filed on February 7, 2017, published on June 8, 2017, and issued on August 29, 2017. (E-SF 25, 29; A-SF ¶ 27, 28; JTX-2 at Cover.)

52. U.S. Patent 9,750,785 ("the '785 Patent") was filed on February 7, 2017, published on June 8, 2017, and issued on September 5, 2017. (E-SF 28–29; A-SF ¶ 30, 31; JTX-3 at Cover.)

53. The '209 and '785 Patents (the "Asserted Patents") are both continuations-in-part of U.S. Application No. 15/289,640, issued as U.S. Patent No. 9,687,526 ("the '526 Patent"), which is a continuation-in-part of U.S. Application No. 14/717,877, issued as U.S. Patent No. 9,744,239 ("the '239 Patent"), which is a continuation of U.S. Application No. 14/610,499, which was abandoned ("the '499 Application"). (E-SF 26, 29, 32; A-SF ¶ 28, 31; JTX-2 at Cover; JTX-3 at Cover.)

54. U.S. Patent No. 9,375,478 ("the '478 Patent") is a continuation of the '499 Application and a sister patent to the '239 Patent. (*See* DTX-7.1, DTX-7.71.)

55. The Asserted Patents are entitled to a priority date of February 7, 2017. (E-SF 27, 30; A-SF ¶ 29, 32; Park Tr. 389:2–6.)

56. Both of the Asserted Patents, as well as the '478 Patent, list Matthew Kenney, Vinayagam Kannan, Sunil Vandse, and Suketu Sanghvi as named inventors. (E-SF 25, 28; A-SF ¶ 27, 30; JTX-2 at Cover; JTX-3 at Cover; DTX-7.5.)

57. The '239 Patent lists Matthew Kenney and Vinayagam Kannan as named inventors. (DTX-605.2.)

B. The Asserted Claims

58. Par asserts that Eagle infringes claims 1, 4, 5, and 7, and that Amneal infringes claims 1, 2, and 4–8 of the '209 Patent, which read as follows:

> 1. A method of increasing blood pressure in a human in need thereof, the method comprising administering to the human a unit dosage form, wherein the unit dosage form comprises from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically acceptable salt thereof, wherein:
>
> the unit dosage form has a pH of 3.7-3.9;
>
> the unit dosage form further comprises impurities that are present in an amount of 0.9% - 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1;
>
> the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and
>
> the human is hypotensive.[2]
>
> 2. The method of claim 1, wherein the impurities comprise SEQ ID NO.: 2, and SEQ ID No.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3%.
>
> 4. The method of claim 1, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.
>
> 5. The method of claim 1, wherein the impurities comprise SEQ ID NO.: 7, and SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%.

[2] Claim 1 of the '209 Patent comprises what are referred to as "Clinical Elements," "Formulation Elements," and "Impurities Elements." (*See, e.g.*, DDX2-7.)

6. The method of claim 1, wherein the impurities comprise SEQ ID NO.: 10, and SEQ ID No.: 10 is present in the unit dosage form in an amount of 0.1%.

7. The method of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

8. The method of claim 7, wherein the impurities further comprise SEQ ID NO.: 3, SEQ ID NO.: 7 and SEQ ID NO.: 10, and SEQ ID No.: 3 is present in the unit dosage form in an amount of 0.1%, SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%, and SEQ ID NO.: 10 is present in the unit dosage form in an amount of 0.1%.

(E-SF 35; A-SF 37.)

59. Par asserts that both Eagle and Amneal infringe claims 1, 5, and 8 of the ’785 Patent, which read as follows:

1. A pharmaceutical composition comprising, in a unit dosage form, from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof, wherein the unit dosage form further comprises impurities that are present in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1, and wherein the unit dosage form has a pH of 3.7-3.9.[3]

5. The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

8. The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3%

[3] Claim 1 of the ’785 Patent comprises what are referred to as “Formulation Elements,” and “Impurities Elements.” (*See*, *e.g.*, DDX2-7.)

and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

(E-SF 36; A-SF ¶ 38) (referred collectively with the ’209 claims as the “Asserted Claims”).

60. As defined in the ’209 and ’785 Patents:

- SEQ ID NO.: 1 refers to vasopressin;
- SEQ ID NO.: 2 refers to Gly9-vasopressin (Gly9);
- SEQ ID NO.: 3 refers to Asp5-vasopressin (Asp5);
- SEQ ID NO.: 4 refers to Glu4-vasopressin (Glu4);
- SEQ ID NO.: 7 refers to Acetyl-vasopressin (Acetyl);
- SEQ ID NO.: 10 refers to D-Asn-vasopressin (DAsn).

(A-SF 39.)

61. Par considers the full scope of the Asserted Claims to include a vasopressin formulation that, even though manufactured to a pH outside the claimed range of 3.7–3.9, including between 3.4 and 3.6, exhibits the claimed pH at any point during its shelf life, even for just a few minutes. (Kirsch Tr. 300:14–18 (“**Q.** . . . I think is it your view that if it went to 3.7 to 3.9 for five minutes, that that would be infringing? **A.** Well, that’s -- yes. I mean, I think literally, that would be infringing, yes.”).)

62. Par considers the full scope of the limitation "a pH of 3.7-3.9" in the Asserted Claims to include any pH from 3.65 to 3.94 based on rounding. (Kirsch Tr. 210:11–21, 850:15–16; Park Tr. 411:18–20.)

63. Defendants applied Par's interpretation of the pH limitations of the Asserted Claims in assessing the validity and enforceability of the Asserted Claims. (Park Tr. 389:16–90:11; Chyall Tr. 565:12–19, 567:10–17.)

64. The claims of the '209 and '785 Patents cover Reformulated Vasostrict, and do not cover Original Vasostrict. (*See* E-SF ¶¶ 34, 58, 61; Kirsch Tr. 863:19–64:5 ("**Q.** And just so I understand your opinion that you are doing here, what you are doing is comparing the reformulated Vasostrict data that's on the slide, right, against original Vasostrict data; is that correct? **A.** That's correct. **Q.** And the context in which you are doing that is that reformulated Vasostrict data here is a representation -- is an embodiment of the claims; right? **A.** Yes, that's correct. **Q.** And original Vasostrict is not covered by the claims; is that right? **A.** Yes, that's correct.")).

65–71. [INTENTIONALLY LEFT BLANK]

V. INVALIDITY

A. Definition of a POSA

72. A POSA is a person who has a Master's, Pharm.D., or Ph.D. in pharmaceutical sciences or a related discipline, with several years' experience in the development

of pharmaceutical dosage forms, including stable aqueous peptide formulations. However, more experience may substitute for lower levels of education, and vice versa. Moreover, a POSA would have access to and collaborate with persons having drug formulation experience, as well as pharmacologists, chemists, biologists, or clinicians. (Park Tr. 388:9–19.)

73. Although Par offers a different definition of a POSA, neither party's experts have suggested that their opinions would change depending on which definition the Court adopts. (Park Tr. 388:20–89:1; Kirsch Tr. 827:14–25.)

74. A POSA would have been able to test the properties of a vasopressin product available on the market, including its pH and impurity levels using routine techniques. (Park Tr. 420:12–22.)

B. Original Vasostrict Prior Art

75. A POSA would have looked to Original Vasostrict and its properties, including its labeled pH range of 3.4 to 3.6, in formulating a vasopressin product as of the priority date. (Park Tr. 395:10–16; Kirsch Tr. 810:5–25, 811:6–12:17.)

76. Original Vasostrict was the "RLD that was available in the market" around the priority date. (Aungst Tr. 174:9–15.)

77. Original Vasostrict was first sold in November 2014. (Park Tr. 396:24–97:4; DTX-86.1; E-SF 16; A-SF ¶ 18.)

78. The ‘209 Patent includes a description of Original Vasostrict in its patent specification. (JTX-2, Col. 12:17–24; Kirsch Tr. 877:10–14.) The patent states that Original Vasostrict contains “acetic acid . . . quantity sufficient to bring pH to ***about*** 3.4 to ***about*** 3.6.” (JTX-2, Col. 12:17–24) (emphases added.)

79. Dr. Kirsch previously testified that when a particular pH range follows the phrase “about,” that pH range may be “broader” than what rounding principles would allow. (Kirsch Tr. 879:1–80:1.) Based on Dr. Kirsch’s testimony, the description of Original Vasostrict, as provided in the ’209 Patent, could include a pH of 3.65 or higher. (Kirsch Tr. 881:11–82:13.) Dr. Kirsch’s interpretation of the claimed pH range of 3.7 to 3.9 includes a pH of 3.65. (Kirsch Tr. 210:2–10.) Therefore, there is overlap between the pH of the prior art Original Vasostrict formulation and the vasopressin formulation claimed in the asserted claims of the Patents-in-Suit, and Dr. Kirsch’s opinions to the contrary are not credible. (See Kirsch Tr. 884:6–20.)

1. Manufactured Lots of Original Vasostrict

80. NDA No. 204485 for Original Vasostrict was supported by data from three registration batches. (Park Tr. 396:18–23; DTX-26.3.)

81. Original Vasostrict Lot 310571 was a registration batch (Park Tr. 415:16–19; DTX-27.34, 36), which Par relied on and submitted data from in support of the NDA submission. (Park Tr. 416:6–10; DTX-45.3, 5.)

82. Over 1,000 vials from Original Vasostrict lot 788435 were sold between October 28, 2015, and November 11, 2015. (Park Tr. 410:21–25; DTX-1362.8–9.)

83. Original Vasostrict lot 788436 was another lot of Original Vasostrict from which over 1,000 vials were sold between November 11 and November 20, 2015. (Park Tr. 418:13–16; DTX-1362.9–10.)

2. Clinical Use of Original Vasostrict

84. Original Vasostrict was indicated to increase blood pressure in adults with vasodilatory shock (*e.g.*, post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (E-SF 15; A-SF ¶ 19; DTX-132.4; Cross Tr. 498:3–10.)

85. The label for Original Vasostrict instructed the use of a starting dose of 0.03 units per minute and a maximum dose of 0.1 units per minute for post-cardiotomy shock and a starting dose of 0.01 units per minute and a maximum dose of 0.07 units per minute for septic shock. (DTX-132.4; Cross Tr. 500:6–17.)

86. Clinicians looked to the labeling for Original Vasostrict for guidance on how to use that product. (Cross Tr. 500:18–21.)

3. Measurable Properties of Original Vasostrict

87. Original Vasostrict comprised 20 units/mL or 0.0377 mg/mL vasopressin, 0.5% chlorobutanol, water for injection, and acetic acid in a 1 mL vial. (DTX-132.5; DTX-26.3; Park Tr. 397:20–98:6.)

88. The labeling for Original Vasostrict disclosed that it was adjusted to pH 3.4 to 3.6 with acetic acid. (DTX-132.5; Park Tr. 397:20–98:6.)

89. The FDA-approved release specification for Original Vasostrict was pH 3.3 to 4.0. (Park Tr. 412:20–24; DTX-26.26.) Thus, a batch of Original Vasostrict that had a pH of 3.7–3.9 could be released per the specifications for that product. (Park Tr. 412:25–13:3; DTX-26.26.)

90. The stability specification for Original Vasostrict was pH 2.5 to 4.5. (Park Tr. 412:20–24; DTX-26.26.) Thus, a batch of Original Vasostrict that had a pH of 3.7–3.9 would be within the stability specification for this product. (Park Tr. 413:4–7; DTX-26.26.)

91. The pH of Original Vasostrict lot 788435 was recorded as 3.6 over its 24-month shelf life. (Park Tr. 414:12–14, Kirsch Tr. 862:4–8; DTX-360.25–26.)

92. The 6-month measurement for Original Vasostrict lot 788435 was recorded on August 23, 2015. (DTX-360.25.)

93. Original Vasostrict lot 788435 had 0.7% total impurities having between 85 and 100% sequence homology to vasopressin on August 23, 2015.

(DTX-360.25.) The total impurities measurement at that time point was 1.5%, when taking into account unidentified impurities. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claim 1 and JTX-3 at claim 1.)

94. Original Vasostrict lot 788435 had 0.2% SEQ ID NO. 2 (Gly9-AVP) on August 23, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 2 in an amount of 0.1% to 0.3% on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 2, 7 and JTX-3 at claim 8.)

95. Original Vasostrict lot 788435 had 0.2% SEQ ID NO. 4 (Glu4-AVP) on August 23, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 4 in an amount of 0.2% to 0.4% on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 4, 7 and JTX-3 at claims 5, 8.)

96. Original Vasostrict lot 788435 had 0.1% SEQ ID NO. 10 (D-Asn-AVP) on August 23, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 10 in an amount of 0.1% on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 6, 8.)

97. Original Vasostrict lot 788435 had 0.2% SEQ ID NO. 7 (Acetyl-AVP) on August 23, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had even

less than 0.3% to 0.6% of SEQ ID NO. 7 on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 5, 8.)

98. Par's testing of Original Vasostrict lot 788435 recorded a "Not Reported" result for SEQ ID NO. 3 (Asp5-AVP) on August 23, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had even less than 0.1% of SEQ ID NO. 3 on August 23, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claim 8.)

99. Original Vasostrict lot 788435 had a pH of 3.6 on August 21, 2015. (Park Tr. 414:12–14, Kirsch Tr. 862:4–8; DTX-360.25–26.)

100. The 9-month measurement for Original Vasostrict lot 788435 was recorded on December 2, 2015. (DTX-360.25.)

101. Original Vasostrict lot 788435 had 0.9% total impurities having between 85 and 100% sequence homology to vasopressin on December 2, 2015. (DTX-360.25.) The total impurities measurement at that time point was 1.8%, when taking into account unidentified impurities. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claim 1 and JTX-3 at claim 1.)

102. Original Vasostrict lot 788435 had 0.2% SEQ ID NO. 2 (Gly9-AVP) on December 2, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had

SEQ ID NO. 2 in an amount of 0.1% to 0.3% on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 2, 7 and JTX-3 at claim 8.)

103. Original Vasostrict lot 788435 had 0.3% SEQ ID NO. 4 (Glu4-AVP) on December 2, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 4 in an amount of 0.2% to 0.4% on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 4, 7 and JTX-3 at claims 5, 8.)

104. Original Vasostrict lot 788435 had 0.1% SEQ ID NO. 10 (D-Asn-AVP) on December 2, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 10 in an amount of 0.1% on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 6, 8.)

105. Original Vasostrict lot 788435 had 0.3% SEQ ID NO. 7 (Acetyl-AVP) on December 2, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 7 in an amount of 0.3% to 0.6% on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claims 5, 8.)

106. Par's testing of Original Vasostrict lot 788435 recorded a "Not Reported" result for SEQ ID NO. 3 (Asp5-AVP) on December 2, 2015. (DTX-360.25.) Thus, Original Vasostrict lot 788435 had even less than 0.1% SEQ ID NO. 3 on December 2, 2015. (*Compare* DTX-360.25 *with* JTX-2 at claim 8.)

107. Original Vasostrict lot 788435 had a pH of 3.6 on December 2, 2015. (Park Tr. 414:12–14, Kirsch Tr. 862:4–8; DTX-360.25–26.)

108. The 12-month measurement for Original Vasostrict lot 788435 was recorded on February 18, 2016. (DTX-360.25; *see also* Kirsch Tr. 858:9–23.)

109. Original Vasostrict lot 788435 had 0.9% total impurities having between 85 and 100% sequence homology to vasopressin on February 18, 2016. (Kirsch Tr. 861:2–18; DTX-360.25.) The total impurities measurement at that time point was 1.7%, when taking into account unidentified impurities. (Kirsch Tr. 861:2–18; DTX-360.25.) Thus, Original Vasostrict lot 788435 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claim 1 and JTX-3 at claim 1.)

110. Original Vasostrict lot 788435 had 0.3% SEQ ID NO. 2 (Gly9-AVP) on February 18, 2016. (Kirsch Tr. 859:21–60:5; DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 2 in an amount of 0.1% to 0.3% on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claims 2, 7 and JTX-3 at claim 8.)

111. Original Vasostrict lot 788435 had 0.3% SEQ ID NO. 4 (Glu4-AVP) on February 18, 2016. (Kirsch Tr. 860:6–7; DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 4 in an amount of 0.2% to 0.4% on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claims 4, 7 and JTX-3 at claims 5, 8.)

112. Original Vasostrict lot 788435 had 0.1% SEQ ID NO. 10 (D-Asn-AVP) on February 18, 2016. (Kirsch Tr. 860:8–9; DTX-360.25.) Thus, Original Vasostrict lot 788435 had SEQ ID NO. 10 in an amount of 0.1% on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claims 6, 8.)

113. Original Vasostrict lot 788435 had 0.2% SEQ ID NO. 7 (Acetyl-AVP) on February 18, 2016. (Kirsch Tr. 860:16–17; DTX-360.25.) Thus, Original Vasostrict lot 788435 had even less than 0.3% to 0.6% SEQ ID NO. 7 on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claims 5, 8.)

114. Par's testing of Original Vasostrict lot 788435 recorded a "Not Reported" result for SEQ ID NO. 3 (Asp5-AVP) on February 18, 2016. (Kirsch Tr. 860:10–15; DTX-360.25.) Thus, Original Vasostrict lot 788435 had even less than 0.1% SEQ ID NO. 3 on February 18, 2016. (*Compare* DTX-360.25 *with* JTX-2 at claim 8.)

115. Original Vasostrict lot 788435 had a pH of 3.6 on February 18, 2016. (Park Tr. 414:12–14, Kirsch Tr. 862:4–8; DTX-360.25–26.)

116. The pH of Original Vasostrict lot 310571 was 3.8 after 18 months of refrigerated storage. (Park Tr. 415:24–16:2; Kirsch Tr. 815:25–16:4; DTX-27.34, 36.) This result was within specification for Original Vasostrict. (Park Tr. 416:3–5; DTX-27.34, 36.)

117. Original Vasostrict lot 310571 had 0.8 and 1.8% total impurities having between 85 and 100% sequence homology to vasopressin at the initial and three month time points, respectively, in room temperature storage. (Park Tr. 416:11–15; DTX-45.7.) The total impurities measurements at these time points were 1.1% and 2.4%, respectively, when taking into account unidentified impurities. (DTX-45.7.) Thus, Original Vasostrict lot 310571 had 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin between the initial and three month time points in room temperature storage. (*Compare* Park Tr. 416:16–20, DTX-45.7 *with* JTX-2 at claim 1 and JTX-3 at claim 1.)

118. Original Vasostrict lot 310571 had 0.1% and 0.5% SEQ ID NO. 2 (Gly9-AVP) at the initial and three month time points, respectively, at room temperature storage. (Park Tr. 417:14–17; DTX-45.7.) Thus, Original Vasostrict lot 310571 had SEQ ID NO. 2 in an amount of 0.1 to 0.3% between the initial and three month time points in room temperature storage. (*Compare* Park Tr. 417:14–17, DTX-45.7 *with* JTX-2 at claims 2, 7 and JTX-3 at claim 8.)

119. Original Vasostrict lot 310571 had "None Detected" and 0.11% SEQ ID NO. 3 (Asp5-AVP) at the initial and three month time points, respectively, at room temperature storage. (Park Tr. 417:14–17; DTX-45.7.) Thus, Original Vasostrict lot 310571 had SEQ ID NO. 3 in an amount of 0.1% between the initial

and three month time points in room temperature storage. (*Compare* Park Tr. 417:14–17, DTX-45.7 *with* JTX-2 at claim 8.)

120. Original Vasostrict lot 310571 had 0.1% and 0.6% SEQ ID NO. 4 (Glu4-AVP) at the initial and three month time points, respectively, at room temperature storage. (Park Tr. 417:14–17; DTX-45.7.) Thus, Original Vasostrict lot 310571 had SEQ ID NO. 4 in an amount of 0.2% and 0.4% between the initial and three month time points in room temperature storage. (*Compare* Park Tr. 417:14–17, DTX-45.7 *with* JTX-2 at claims 4, 7 and JTX-3 at claims 5, 8.)

121. Original Vasostrict lot 310571 had 0.25% and 0.26% SEQ ID NO. 7 (Acetyl-AVP) at each of the initial and three month time points at room temperature storage. (Park Tr. 417:14–17; DTX-45.7.) Thus, Original Vasostrict lot 310571 had SEQ ID NO. 7 in an amount of 0.3% and 0.6% between the initial and three month time points in room temperature storage. (*Compare* Park Tr. 417:14–17, DTX-45.7 *with* JTX-2 at claims 5, 8.)

122. Original Vasostrict lot 310571 had a pH of 3.5 at the time of initial testing. (DTX-45.7; Park Tr. 415:16–16:2.)

123. Original Vasostrict lot 310571 had a pH of 3.5 after three months of room temperature storage. (DTX-45.7.)

124. Original Vasostrict lot 310571 had a pH of 3.8 after eighteen months of refrigerated storage. (Park Tr. 415:16–16:10; DTX-27.34, 36; Kirsch Tr. 815:10–16:4.)

125. A POSA would expect that a vasopressin formulation would have lower impurities under refrigeration due to slower degradation. (Kirsch Tr. 849:20–50:1.)

126. Original Vasostrict lot 788436 had a pH of 3.7 at the time of release testing. (Park Tr. 417:24–18:10; DTX-1314.1; *see also* Kirsch Tr. 822:22–23:09.)

127. Original Vasostrict lot 788436 had 0.7% total impurities having between 85 and 100% sequence homology to vasopressin at the time of release testing. (Park Tr. 418:17–19:11; DTX-1314.1.) This lot had 1.6% total impurities at that time point, when taking into account unidentified impurities. (Park Tr. 418:17–19:11; DTX-1314.1.) Thus, Original Vasostrict lot 788436 had even less than 0.9 to 1.7% impurities having between 85 and 100% sequence homology to vasopressin at the time of release testing. (*Compare* Park Tr. 418:17–19:11, DTX-1314.1 *with* JTX-2 at claim 1 and JTX-3 at claim 1.)

128. Original Vasostrict lot 788436 had 0.1% SEQ ID NO. 2 (Gly9-AVP) at time of release testing. (DTX-1314.1.) Thus, Original Vasostrict lot 788436 had SEQ ID NO. 2 in an amount of 0.1% to 0.3% at the time of release testing. (*Compare* DTX-1314.1 *with* JTX-2 at claims 2, 7 and JTX-3 at claim 8.)

129. Release testing for Original Vasostrict lot 788436 recorded a "None Detected" result for SEQ ID NO. 3 (Asp5-AVP). (DTX-1314.1.) Thus, Original Vasostrict lot 788436 had even less than 0.1% SEQ ID NO. 3 at the time of release testing. (*Compare* DTX-1314.1 *with* JTX-2 at claim 8.)

130. Release testing for Original Vasostrict lot 788436 recorded a "Not Reported" result for SEQ ID NO. 4 (Glu4-AVP). (DTX-1314.1.) Thus, Original Vasostrict lot 788436 had even less than 0.2% to 0.4% SEQ ID NO. 4 at the time of release testing. (*Compare* DTX-1314.1 *with* JTX-2 at claims 4, 7 and JTX-3 at claims 5, 8.)

131. Original Vasostrict lot 788436 had 0.4% SEQ ID NO. 7 (Acetyl-AVP) at time of release testing. (DTX-1314.1.) Thus, Original Vasostrict lot 788436 had SEQ ID NO. 7 in an amount of 0.3% to 0.6% at the time of release testing. (*Compare* DTX-1314.1 *with* JTX-2 at claims 5, 8.)

4. Eagle's Proposed ANDA Product

132. Eagle submitted ANDA No. 211538 ("Eagle's ANDA") pursuant to 35 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of a proposed generic vasopressin product, Vasopressin Injection USP, 20 units/1 mL ("Eagle's Proposed ANDA Product"), identifying VASOSTRICT as the reference listed drug. (E-SF 39.)

133. Eagle has specified Original Vasostrict as the Reference Listed Drug ("RLD") for its proposed ANDA Product. (DTX-131.1; Park Tr. 348:16–20.)

134. The effective filing date of the '209 and '785 Patents is February 7, 2017. (E-SF 27, 30; A-SF ¶ 29, 32.) The '209 Patent was issued on August 29, 2017 and was published on June 8, 2017. (JTX-2.) The '785 Patent was issued on September 5, 2017 and was published on June 8, 2017. (JTX-3.)

135. Registration batch SVA001 was manufactured by Albany Molecular Research Inc. ("AMRI") on March 3, 2017. (E-SF 44–45.) As of March 3, 2017, the release pacification and stability specification for SVA001 with respect to pH was 2.5 to 4.5. (DTX-288.1.) As of March 3, 2017, the '209 and '785 Patents had not published, and had not issued. (JTX-2; JTX-3.)

136–150. [INTENTIONALLY LEFT BLANK]

C. The Asserted Claims Are Obvious Over Original Vasostrict as Sold with its Labeling

1. Original Vasostrict as Sold and Used Satisfied All Elements of the Claims with an Abutting or Overlapping pH

151. Original Vasostrict was sold and in public use with a label instructing the practice of the method of treatment limitations of the '209 Patent. (E-SF 15; DTX-132.4; Cross Tr. 498:3–10, 500:6–17.)

152. Original Vasostrict was sold and in public use as a unit dosage form comprising between 0.01 and 0.07 mg/mL vasopressin. (DTX-132.5; DTX-26.3; Park Tr. 397:20–98:6.)

153. Original Vasostrict was sold and in public use with pH 3.6 and between 0.9% and 1.7% total impurities having between 85% and 100% sequence homology to vasopressin. (Park Tr. 418:17–19:11; Kirsch Tr. 861:2–18; DTX-360.25; DTX-1314.1.) Original Vasostrict was sold and in public use with pH 3.6 and impurities that satisfied the dependent claim limitations as well. (Park Tr. 420:5–11.) A pH 3.6 abuts the pH range of the asserted claims. (Park Tr. 414:12–14; 419:20–20:4.)

154. The labeled pH range for Original Vasostrict—3.4 to 3.6—abuts that of the asserted claims. (Park Tr. 411:9–22; Kirsch Tr. 807:13–21, 815:3–6 ("**Q.** What do those labels say about the pH of original Vasostrict? **A.** It indicates that the pH would adjust with acetic acid at 3.4 to 3.6."); DTX-132.5.)

155. Original Vasostrict was sold and in public use at a pH of 3.6, which abuts the pH range of the asserted claims. (Park Tr. 414:12–14; 419:20–20:4.)

156. The pH range for Original Vasostrict in the prior art includes values up to 3.64 through the application of rounding principles. (Park Tr. 411:21–22; Kirsch Tr. 850:12–14, 881:6–10.)

157. Par has asserted that a product having pH 3.6 over its shelf life except for five minutes at pH 3.7 is within the scope of the asserted claims. (Park Tr. 389:16–90:4; Kirsch Tr. 300:14–18.)

158. A POSA at the Asserted Patent priority date would not have expected to be able to detect any difference between the stability of a vasopressin formulation with a pH of 3.64, at the upper end of the Original Vasostrict label pH range of 3.4–3.6, and that of a vasopressin formulation with a pH of 3.65, at the lower end of the claimed pH range of 3.7–3.9. (Park Tr. 411:23–12:16; Kirsch Tr. 853:12–15, 850:25–51:5 ("**Q.** And so I take it that you would agree that it would be hard to discern the difference in stability between a formulation with a pH of 3.64 versus 1 of 3.65? **A.** Yes. I would add to that that it would even be hard to do the experiment to observe the difference with that degree of separation.").)

159. The sale and public use of Original Vasostrict with its label and properties, including its impurity levels and abutting pH, would have rendered the claimed methods and formulations in the Asserted Claims obvious. (Park Tr. 419:12–20:11.)

2. A POSA Would Have Achieved the Claimed Invention by Making Original Vasostrict As A Matter Of Course

160. A POSA adopting the Original Vasostrict formulation as of the Asserted Patent priority date would not have been concerned about pH drifting within the shelf life specification of 2.5–4.5, including into the claimed range of 3.7–

3.9. (Park Tr. 421:23–22:20; *see also* PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742; Kirsch Tr. 813:9–12 ("**Q.** So was the stability of a product with a known range of 2.5 to 4.5 considered to be a problem in the prior art? **A.** No.").)

161. Original Vasostrict was permitted to drift outside of the pH 3.4 to 3.6 range over shelf life. (Park Tr. 412:20–24; Kirsch Tr. 815:20–16:11; DTX-26.26.)

162. A POSA would have expected a vasopressin formulation based on Original Vasostrict to maintain low impurities under refrigeration. (Kirsch Tr. 849:20–50:1.) The label for Vasostrict instructs to store the product at refrigerated temperatures. (Park Tr. 504:9–11; DTX-132.5, § 16; DTX-151.4, § 16.)

163. Consistent with its stability specifications, Original Vasostrict drifted outside of the pH range of 3.4 to 3.6 at release and over shelf life. (Park Tr. 415:24–16:2, 417:24–18:10; Kirsch Tr. 815:20–16:11; DTX-27.34, 36; DTX-1314.1.)

164. A POSA would not have expected there to be any difference in the stability between a formulation at pH 3.4 to 3.6 and one that drifted into the claimed range over shelf life. (Park Tr. 411:23–12:16; Kirsch Tr. 853:12–15; Vandse Tr. 678:3–21.)

165. Original Vasostrict as sold and in public use satisfied the method of treatment, vasopressin concentration, unit dosage form, and impurities limitations of the asserted claims. (FF ¶¶ 136–153.) A POSA making a formulation based on the

Original Vasostrict prior art who allowed the formulation to drift within its shelf life pH specification to the claimed pH range would have achieved the claimed inventions as a matter of course.

D. There Are No Secondary Considerations of Non-Obviousness

1. The Claimed pH Range is Not Critical to Stability

a. Par Failed to Show Criticality of the Claimed pH Range Across Full Scope of the Asserted Claims

166. Dr. Kirsch conceded that it would be difficult to discern the difference in stability between a formulation with a pH of 3.65 versus a formulation with a pH of 3.64. (Kirsch Tr. 850:25–51:5 ("**Q.** And so I take it that you would agree that it would be hard to discern the difference in stability between a formulation with a pH of 3.64 versus 1 of 3.65? **A.** Yes. I would add to that that it would even be hard to do the experiment to observe the difference with that degree of separation.").)

167. Named Inventor Matthew Kenney was unable to identify a critical difference in stability of vasopressin formulations that have the pH of 3.6 compared to pH of 3.8. (Kenney Tr. 548:14–23 ("**Q.** Is there a critical difference in stability to Vasopressin formulations between the pH of 3.8 and pH of 3.6? **A.** Critical is subjective. And either way, we would have to do the study with only those two variables changed. **Q.** Have you performed such study with regard to the original Vasostrict? **A.** Original Vasostrict, no, not as far as I recall.").)

168. Dr. Kirsch conceded it would be difficult to discern the difference in stability between a formulation with a pH of 3.65 versus a formulation with a pH of 3.64 throughout the shelf-life that drifts into pH 3.65 for five minutes. (Kirsch Tr. 851:17–53:8 (". . . . **Q.** A POSA would have no expectation of any difference whatsoever in what I described 25 C. Fair? **A.** It would be difficult to see any difference, that's correct.").)

169. Named Inventor Sangvhi was unaware of any data demonstrating any benefit of a vasopressin formulation that has a pH 3.4 to 3.6 at release that drifts into pH 3.8 during shelf life:

> **Q.** Are you aware of any data whatsoever showing the benefit of having a pH that starts within the range of 3.4 to 3.6 at release, but then goes up to 3.8 during the shelf life?
>
> **A.** I don't recall such data.

(Sanghvi Tr. 687:23–88:2.)

170. Named Inventor Kenney did not know whether a vasopressin formulation that starts at pH 3.5 that drifts to pH 3.8 at 18 months would show any stability benefit:

> **Q.** And do you recall reviewing one of the stability tables for the original Vasostrict which started at pH of 3.5 and then "spiked" to pH 3.8 at 18 months?
>
> A. Yes. I don't know if "spiked" is the correct term, but yes, I remember that data table.
>
> **Q.** So at that pH at 18 months, would that Vasopressin formulation be more stable than when it started out with by the virtue of the pH?

A. I don't know. We would have to run that study.

(Kenney Tr. 551:1–11.)

171. Named Inventor Vandse was unaware of any data demonstrating any benefit of a vasopressin formulation that has a pH 3.4 to 3.6 at release that drifts into pH 3.8 during shelf life:

> **Q.** And based on the studies you performed and the conclusions you reached, a batch that's designed to have a pH of 3.4 to 3.6 on release, but that subsequently drifts to a pH of 3.8, would not achieve the improvement in assay and impurities stability that you have found studies, correct?
>
> **A.** I do not recall having performed any such studies where the batch was made with 3.4 to 3.6 pH and then made to drift to 3.8 and then evaluated the stability profile.

(Vandse Tr. 678:3–12.)

b. Par's Comparisons Involving Reformulated Vasostrict Do Not Demonstrate Criticality

172. Dr. Kirsch compared stability data from Reformulated Vasostrict (which was intended to represent the claimed vasopressin formulation) with that of Original Vasostrict and Eagle's ANDA Product (which were intended to represent formulations outside the claims). (Chyall Tr. 605:16–25; Kirsch Tr. 863:24–64:5.)

173. [WITHDRAWN BASED ON CORRECTIONS TO THE TRIAL TRANSCRIPT]

174. As part of his comparison, Dr. Kirsch opined that Reformulated Vasostrict had 3.5% increase in impurities over its 12-month room temperature shelf

life, compared to 4.5% increase for Original Vasostrict and 5.5% increase for Eagle's ANDA Product. (Kirsch Tr. 864:13–65:21.)

175. Impurities of 3.5, 4.5, and 5.5% are all well below the 17% total impurities allowable during the shelf-life of Reformulated and Original Vasostrict, based on these products' stability specifications. (Kirsch Tr. 865:22–66:5; Chyall Tr. 608:12–18.)

176. Impurities of 3.5 and 4.5% are below the impurities specification of 5% at release for Reformulated and Original Vasostrict. (Kirsch Tr. 864:24–65:3; DTX-72.2).

177. Because there is only a 1–2% difference in impurities over 12 months at room temperature, any difference in stability demonstrated by the comparison of Reformulated Vasostrict to Original Vasostrict and Eagle's ANDA Product is at most a difference in degree, not kind. (*See* FF 174–175.)

178. Dr. Kirsch did not identify any practical difference in safety or otherwise associated with the differences in impurity levels he identified. (*See* Kirsch Tr. 864:24–65:3.) Rather, he admitted that Original Vasostrict was safe. (Kirsch Tr. 863:7–9.)

179. There have been no changes in the storage and use of Vasostrict since the introduction of Original Vasostrict, including after the introduction of Reformulated Vasostrict. (Cross Tr. 495:5–8; *see* Coralic Tr. 142:16–44:4.)

180. There is no safety advantage between Reformulated Vasostrict and Original Vasostrict. (Vandse Tr. 679:25–80:4; *see also* Coralic Tr. 144:2–15; 144:25–45:21; Cross Tr. 495:5–8.) Dr. Coralic was not aware that a reformulation had occurred prior to being retained for this case. (Coralic Tr. 142:10–25.) Dr. Cross testified that the manner in which vasopressin is used has not changed during his practice, which spans over 40 years. (Cross Tr. 495:5–8.)

181. Dr. Kirsch's comparisons do not evaluate criticality of the claimed pH over the full scope of the claims because Reformulated Vasostrict is formulated to have an initial pH at or near 3.8, not 3.7 or 3.9. (Chyall Tr. 606:5–19.)

182. Dr. Kirsch's comparison does not examine pH stability for formulations that start at a pH outside of the claimed range, but drift into the claimed pH range over time, consistent with Par's interpretation of the Asserted Claims. (Chyall Tr. 606:5–19; FF 61, 214; Kirsch Tr. 867:21–68:3 ("**Q.** So have you seen any study anywhere, whether what was submitted to the Patent Office, any of the references you've identified for teaching away or anywhere elsewhere somebody compared the stability of a formulation that was at 3.4 to 3.6, right, for its life compared to one that was 3.4 to 3.6 throughout its life except for a five-minute time in the range 3.7 to 3.9? **A.** I have not seen that study.").)

183. Reformulated Vasostrict differs from Original Vasostrict and Eagle's ANDA Product in that Reformulated Vasostrict "does not contain any

chlorobutanol," but does contain "sodium acetate buffers . . . [s]odium hydroxide and hydrochloric acid." (Chyall Tr. 606:20–07:9.)

184. Because Reformulated Vasostrict has a different formulation than Original Vasostrict and Eagle's ANDA Product, "it's not possible to attribute any difference in performance [to] just pH, because there are other variables in these products." (Chyall Tr. 606:20–07:15, 607:19–24; DTX-65.8; *see also* Kenney Tr. 551:12–52:17.)

185. Although Par's witnesses testified that Par possesses data that shows Reformulated Vasostrict could have less impurities and a longer shelf life than Original Vasostrict and Eagle's ANDA Product, Par did not produce that data in Court nor submit it to the FDA for consideration, and both Original and Reformulated Vasostrict have the same shelf life and impurities specifications. (Chyall Tr. 608:8–18; Kirsch Tr. 849:2–5.) Specifically, both Original and Reformulated Vasostrict have 24-month shelf-life under refrigeration, and 12-month shelf-life in room temperature. (Kannan Tr. 522:17–23:4, 713:16–14:9; Kirsch Tr. 849:2–5, Chyall Tr. 608:8–11.)

186. Even if data shows that Reformulated Vasostrict could have a longer shelf life than Original Vasostrict or Eagle's ANDA Product, that does not show criticality of the claimed pH "because there are other differences other than pH," such as differences between the formulations. (Chyall Tr. 608:19–23; FF 183–184.)

Named Inventor Kenney testified that he would not be "comfortable" in concluding that any stability difference between Reformulated Vasostrict and Original Vasostrict is due to the difference in pH "based on the non-controlled variables." (Kenney Tr. 551:12–52:17.)

187. The fact that Reformulated Vasostrict has a pH specification of 3.6–4.0 at release, and 2.5–4.5 over the shelf life means that Reformulated Vasostrict does not need to have a pH of 3.7–3.9 at any time from release through its shelf life, thus undermining any alleged criticality of the claimed pH range. (Chyall Tr. 609:13–10:3; DTX-72.1.)

c. Par's pH Stability Studies Do Not Demonstrate Criticality of the Claimed pH Range

188. The named inventors of the Asserted Patents conducted two stability studies testing vasopressin solutions adjusted to pH 2.5 to 4.5 in 0.1 pH unit increments (the "pH stability studies"). (Chyall Tr. 560:10–17, 575:17–76:23; JTX-2 at PAR-VASO_0295288; JTX-3 at PAR-VASO_0295449–50.)

189. The inventors relied on the results of the pH stability studies to argue that the pH ranges and values claimed in the '478, '239, '209, and '785 Patents are critical to overcome prior art rejections before the Patent Office. (Chyall Tr. 567:23–68:6; DTX-7.1893–96 ('478 Patent); DTX-10.2369–70 ('239 Patent); JTX-2 at PAR-VASO_0295288 ('209 Patent); JTX-3 at PAR-VASO_0295449–50 ('785 Patent).)

190. Although originally presented to the Patent Office through inventor declarations in earlier prosecutions, the pH stability studies were later incorporated into the specifications of the ’209 and ’785 Patents in Examples 9 and 10. (Chyall Tr. 567:23–68:6; JTX-2 at PAR-VASO_0295288 (’209 Patent); JTX-3 at PAR-VASO_0295449–50 (’785 Patent).)

191. The pH stability studies do not demonstrate the criticality of the claimed pH 3.7–3.9. (Chyall Tr. 564:20–23; JTX-2 at PAR-VASO_0295288–89 at 97:41–99:15; JTX-3 at PAR-VASO_0295449–50 at 96:41–98:36; FF 192–211.)

i. The pH Stability Studies Do Not Cover the Full Scope of the Claims

192. The pH stability studies were conducted using formulations comprising 20 units/mL vasopressin in water along with a ten-millimolar acetate buffer adjusted to a particular initial pH. (Chyall Tr. 573:14–20; JTX-2 at PAR-VASO_0295288; JTX-3 at PAR-VASO_0295449–50.)

193. The pH stability studies compared vasopressin formulations having different ***initial*** pHs. (Chyall Tr. 568:7–14 (“[W]hat Par scientists did was they prepared a solution of Vasopressin and then adjusted it to a particular pH and then the results obtained were always related back to the initial pH of the experiment.”); Vandse Tr. 677:21–78:2; Sanghvi Tr. 687:23–88:2.)

194. The pH stability studies did not evaluate formulations manufactured at one pH that drifted to another pH during the shelf life. (Chyall Tr. 569:1–5; Kirsch

Tr. 867:21–68:3; FF 61; Kenney Tr. 551:1–23; Vandse Tr. 678:3–21 ("I do not recall having performed any such studies where the batch was made with 3.4 to 3.6 pH and then made to drift to 3.8 and then evaluated the stability profile."); Sanghvi Tr. 687:23–88:2.)

195. The pH stability studies did not evaluate criticality of the claimed pH over the full scope of the Asserted Claims as interpreted by Par for infringement because they did not evaluate the stability of formulations that start with a pH outside of the claimed range of 3.7–3.9, that then drift into the claimed pH range during the shelf life. (Chyall Tr. 567:18–22, 568:19–25; FF 61; Vandse Tr. 678:3–21 ("I do not recall having performed any such studies where the batch was made with 3.4 to 3.6 pH and then made to drift to 3.8 and then evaluated the stability profile."); Sanghvi Tr. 687:23–88:2.)

196. The selection and concentration of a particular buffer can affect the stability of vasopressin formulations "in a manner that cannot be predicted." (DTX-7.2165–66; Chyall Tr. 574:10–16, 574:21–75:1; Kenney Tr. 547:17–48:2, 551:12–52:17.)

197. The Asserted Claims do not require any particular buffer, or any buffer at all. (Chyall Tr. 573:21–74:1; JTX-2 at PAR_VASO_0295297–98; JTX-3 at PAR-VASO_0295458–59.) The type of buffers used in vasopressin formulations can impact stability. (Kenney Tr. 547:23–48:2 ("**Q.** Okay. Is the pH of 3.8 the most

stable pH regardless of the type of buffers or components used in Vasopressin formulations? **A.** Yeah, we can't say that unless we studied all buffers.").)

198. The Asserted Claims include no limitation as to the excipients that may be used in a vasopressin formulation. (Chyall Tr. 573:21–74:1; JTX-2 at PAR_VASO_0295297–98; JTX-3 at PAR-VASO_0295458–59.)

199. The pH stability studies did not evaluate criticality of the claimed pH over the full scope of the Asserted Claims with respect to the formulation used because the pH stability studies tested only vasopressin formulations with an acetate buffer, but the Asserted Claims do not require a buffer, or specify any particular buffer. (Chyall Tr. 573:21–74:1, 575:5–10; Kenney Tr. 551:12–52:17.)

ii. The pH Stability Studies Did Not Show a Critical Difference in Formulation Stability for the Claimed pH Range

200. The pH stability studies represent the stability of vasopressin formulations by measuring (1) total impurities; and (2) relative decrease in assay (or the amount of vasopressin in the formulation) at two different temperatures: 25° and 40°C. (Chyall Tr. 575:17–76:6; DTX-10.2362–65; JTX-2 at PAR-VASO_0295288–89 (col. 97:41–99:15); JTX-3 at PAR-VASO_0295449–50 (col. 96:41–98:36).)

201. The data from the pH stability studies show vasopressin formulations are stable across a pH range that is broader than the claimed pH range of 3.7–3.9.

(Chyall Tr. 577:8–18, 580:2–15, 583:13–18, 590:1–6, 590:17–23, 591:2–7 (analyzing impurities and assay data at both 25° and 40°C to conclude that "when you look at the data as a whole, there's no showing of criticality."); *see also* DDX4-15–18; Chyall Tr. 585:18–86:3 (noting blue blocks shown on slides are "the values that [Dr. Chyall] considered to be comparable" for each set of data); DTX-10.2362–65; JTX-2 at PAR-VASO_0295288–89 (col. 97:41–99:15); JTX-3 at PAR-VASO_0295449–50 (col. 96:41–98:36).)

202. Any difference in the stability of vasopressin formulations demonstrated by the pH stability studies is at most a difference in degree, not kind, across the full range of pH 2.5–4.5. (*See* FF 201.)

203. Any difference in properties between a vasopressin formulation that had a pH of 3.64 (which rounds to 3.6) and another vasopressin formulation that had a pH of 3.65 (which rounds to 3.7), would "be so small" that a POSA "wouldn't be able to detect it." (Kirsch Tr. 853:12–15.)

204. Statistical significance means only that the difference between two measurements is "a real difference," rather than "one that maybe [] attributable to random error in the measurement process." (Kirsch Tr. 854:4–8.)

205. Dr. Kirsch conflates statistical significance with criticality, and failed to explain why a statistically significant difference in impurities for the claimed pH

values means those pH values are necessarily critical to stability. (Kirsch Tr. 854:9–55:6.)

206. Even accepting Dr. Kirsch's statistical analysis, that analysis showed that a pH of 4.0, which is outside the claimed range, did not produce a statistically significant difference in impurities compared to the claimed pH range. (Kirsch Tr. 856:21–57:1.)

207. Dr. Kirsch relied on Dr. Marais' statistical analysis as part of his criticality opinions. (Kirsch Tr. 871:15–18.)

208. Dr. Kirsch does not have a degree in statistics, and was not proffered as an expert in biostatistical methods or statistical analysis. (Kirsch Tr. 868:10–14.)

209. Dr. Marais is an expert in biostatistical methods and analysis. (Kirsch Tr. 868:15–17.) Dr. Marais' statistical analysis is sound and reliable and of the type that Dr. Kirsch himself uses and relies upon in the course of his own research. (Kirsch Tr. 868:15–17; 868:21–24; 787:22–88:1.)

210. Dr. Marais' statistical analysis demonstrated that there is no statistically significant difference in the rates of change in impurities levels between vasopressin formulations at pH 3.6 and pH 3.7. (Kirsch Tr. 870:18–23; PDX6-25.) Dr. Marais' analysis further demonstrated that there is no statistically significant difference between vasopressin formulations at pH 3.6 and pH 3.9. (Kirsch Tr. 871:8–14; PDX6-25.) Dr. Marais' analysis is consistent with named inventor Sunil Vandse's

analysis that at 40 degrees, the vasopressin assay for pH 3.6 and pH 3.8 formulations are similar and not statistically significantly different. (Kirsch Tr. 875:10–14; 873:10–74:1; DTX-7.1885[4] ¶ 14.)

211. Par has alleged before the U.S. Patent and Trademark Office that the pH stability studies show the criticality of three distinct pH ranges or values in different patent prosecutions: (1) 3.5–4.1 ('239 Patent, DTX-10.2341–42); (2) 3.7–3.9 ('209 Patent, JTX-8 at PAR-VASO-0005816–17; '785 Patent, JTX-9 at PAR-VASO-0009721–22); and (3) 3.8 ('478 Patent, DTX-7.1867–69; '526 Patent, JTX-7 at PAR-VASO-0004868–69.)

2. The Prior Art Does Not Teach Away from the Claimed pH Range

212. None of the prior art identified by Par teaches away from the claimed pH range of 3.7–3.9, particularly as broadly as Par is construing the claims. (Park Tr. 421:5–10 ("**Q.** Do you agree with [Dr. Kirsch], the references teach away from the claimed invention? **A.** No. I have not seen any, any evidence, any document that indicates that it teaches away from having a formulation that has a pH only for a few minutes during storage.").)

[4] DTX-69 and DTX-7.1883–96 both refer to the same declaration by named inventor Sunil Vandse that was submitted during prosecution. (*See* PDX6-11 (citing "DTX-7.1883-96 (aka DTX-69 (PAR-VASO_0002304)).").)

213. Dr. Kirsch conceded, as of the priority date, POSAs did not consider stability of vasopressin formulations with a pH range of 2.5 to 4.5 to be a problem. (Kirsch Tr. 813:9–12, ("**Q.** So was the stability of a product with a known range of 2.5 to 4.5 considered to be a problem in the prior art? **A.** No.").) Consistently, Dr. Chyall testified that there is "a broad range of stability" for vasopressin around pH 3.5. (Chyall Tr. 613:25–614:23.)

214. Dr. Kirsch provided no evidence that there was any teaching away from a vasopressin formulation that is formulated to pH 3.4 to 3.6 that at some point during the product's shelf-life drifts into the claimed pH range of 3.7 to 3.9 for five minutes:

> **Q**. So have you seen any study anywhere, whether what was submitted to the Patent Office, any of the references you've identified for teaching away or anywhere elsewhere somebody compared the stability of a formulation that was at 3.4 to 3.6, right, for its life compared to one that was 3.4 to 3.6 throughout its life except for a five-minute time in the range 3.7 to 3.9?
>
> **A**. I have not seen that study.

(Kirsch Tr. 867:21–68:3; *see also* Park Tr. 421:5–10.)

215. POSAs would not have been taught away from using vasopressin formulations with a pH of 3.65, as compared to vasopressin formulations with a pH of 3.64. Dr. Kirsch conceded it would be even difficult to "discern the difference in stability between a formulation with a pH of 3.64 versus 1 of 3.65." (Kirsch Tr. 853:9–15, 850:25–51:16.) Dr. Kirsch further conceded it would be difficult to

design an experiment that could "observe the difference with that degree of separation." (Kirsch Tr. 853:9–15, 850:25–51:16.)

216. Vasopressin formulations were already sold at the claimed pH of 3.7–3.9 as of the priority date; as such, the prior art did not teach away from the claimed pH range:

- The USP monograph published in 2009 taught a POSA that vasopressin formulations could have a pH between 2.5 and 4.5. (Park Tr. 392:10–15, 392:21–93:1; DTX-135.3–4.)
- Lithuanian Patent No. 4487, which was published in 1999, described a vasopressin formulation with a pH of 3.80–3.95. (DTX-144.3; Park Tr. 423:9–14; Kirsch Tr. 830:21–31:2.)
- Additionally, vials of Pitressin and Original Vasostrict were sold with a pH between 3.7 and 3.9. (Park Tr. 423:15–24:1; *see* DTX-188.6 (Pitressin); DTX-27.34, 36 (Original Vasostrict).)

217. While Dr. Kirsch testified that a POSA would have ignored Lithuanian Patent No. 4487 because it related to animal-derived vasopressin, (Kirsch Tr. 831:22–25), Dr. Kirsch's testimony was not supported by any evidence, (Kirsch Tr. 832:6–19, 894:11–95:4.)

218. Animal-derived and synthetic vasopressin have the same vasopressin molecule, and the only difference between the two sources that Dr. Kirsch identified

is the starting impurity profile. (Kirsch Tr. 893:12–20, 894:11–95:4 (noting "the [vasopressin] molecules are the same, but it's what comes with the molecule that is different.").)

219. Dr. Kirsch did not testify as to what impact different starting impurity profiles would have on vasopressin stability at different pHs. (*See* Kirsch Tr. 892:22–95.4 (testifying, without support, that "the manufacturing of the API [] would create different sets of problems, different sets of issues for the animal derived versus the synthetic.").)

220. Although the FDA Biopharmaceutics and Chemistry Reviews state that pH of 3.4–3.6 is "critical" because vasopressin degradation "accelerates" at pHs outside that range (PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742), those documents concerned only the initial pH of vasopressin formulations, not formulations that start at a pH outside of the claimed range, but drift into the claimed pH range over time, consistent with Par's interpretation of the Asserted Claims. (Park Tr. 422:3–20; PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742; FF 61.)

221. The FDA Biopharmaceutics and Chemistry Review are FDA documents relating to Original Vasostrict. (PTX-146 at EAGLEVAS0014351; PTX-309 at PAR-VASO_0238741; Park Tr. 421:11–17.) The FDA-approved release specification for Original Vasostrict was pH 3.3 to 4.0, (Park Tr. 412:20–24;

DTX-26.26), and the stability specification for Original Vasostrict was pH 2.5 to 4.5. (Park Tr. 412:20–24; DTX-26.26.) Thus, FDA Biopharmaceutics and Chemistry Review could not teach away from vasopressin formulations that have the initial pH of 3.4 to 3.6 that drifts into the pH of 3.7 to 3.9.

222. The FDA Biopharmaceutics Review and Chemistry Review do not teach away from vasopressin formulations with a pH of 3.7–3.9 because they did not include any accompanying data to show, for instance, how much vasopressin degradation "accelerates" at values right around 3.4–3.6, rendering their conclusions speculative, "vague[,] and uncertain." (Park Tr. 422:3–20; PTX-146 at EAGLEVAS0014353; PTX-309 at PAR-VASO_0238742.)

223. The Bi reference does not teach away from vasopressin formulations with a pH of 3.7–3.9 because it concerned the stability of vasopressin formulations with specific buffers, and in particular phosphate buffers, but different buffers can produce different stability profiles. (Kirsch Tr. 866:10–19; DTX-173.4; *see also* FF 196; Kenney Tr. 547:23–48:2 (named inventor Kenney testifying that one cannot generalize pH study results across formulations "regardless of the type of buffers or components used in Vasopressin formulations" "unless we studied all buffers.").)

224. Bi addressed only formulations manufactured to a particular pH. (*See* Kirsch Tr. 808:10–09:9.)

225–240. [INTENTIONALLY LEFT BLANK]

VI. UNENFORCEABILITY

A. Inequitable Conduct Through Submission Of The False Inventorship Declaration During Prosecution of the '239 Patent

241. The '239 Patent claims priority to U.S. Application No. 14/610,499 (the "'499 Application"), filed January 30, 2015. (DTX-605.2.) The application that issued as the '239 Patent was filed at the PTO on May 20, 2015, as U.S. Application No. 14/717,877 (the "'877 Application"). (DTX-605.2.) The '877 Application is a continuation of the '499 Application and shares a specification with the '499 Application. (DTX-605.2.)

242. The named inventors of the '239 Patent are Matthew Kenney and Vinayagam Kannan. (DTX-605.2.)

243. Craig Kenesky was retained by Par Pharmaceutical Inc. to prosecute the '239 Patent at the PTO. (DTX-10.2, 20, DTX-605.2.)

244. Christina Bradley was the examiner of record during prosecution of the '239 Patent at the PTO. (DTX-605.2.)

1. Disqualifying the April 2014 Vasostrict Label As Prior Art

245. On October 21, 2015, Examiner Bradley issued a Final Office Action rejecting all pending claims of the '877 Application as both anticipated and obvious over the April 2014 Vasostrict® Label. (DTX-10.1871–77.)

246. At the time of the rejection, pending independent claim 16 recited:

> 16. A method of increasing blood pressure in a human in need thereof, the method comprising:

> a) providing a pharmaceutical composition for intravenous administration comprising, in a unit dosage form: i) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof; ii) chlorobutanol; iii) acetic acid; and iv) water, wherein the unit dosage form has a pH of 3.4 to 3.6;
>
> b) storing the unit dosage form at 2-8 °C; and
>
> c) administering the unit dosage form to the human;
>
> wherein:
>
> the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and
>
> the human is hypotensive.

(DTX-10.612; *see also* Kenesky Tr. 663:3–11.)

247. In the October 21, 2015 rejection, Examiner Bradley relied upon various portions of the April 2014 Vasostrict® Label, including the description of the Vasostrict® formulation, its indication, and its method of administration, as follows:

> The [April 2014 Vasostrict® Label] teaches a method to increase blood pressure in adults with vasodilatory shock (e.g. post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines (section 1) comprising:
>
> a) providing a pharmaceutical composition containing vasopressin for intravenous administration in a unit dosage form that contains vasopressin at 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and water for Injection, and a pH adjusted with acetic acid to pH 3.4 – 3.6 (section 11);

> diluting the vasopressin unit dosage form with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration (section 2.1);
>
> b) refrigerating the diluted solution for up to 24 hours (section 2.1); and
>
> c) administering the vasopressin by intravenous route at a dose of 0.03 to 0.1 units/minute for post-cardiotomy shock … or 0.01 to 0.07 units/minute for septic shock (section 2.2).

(DTX-10.1874; *see also* Kenesky Tr. 663:3–65:1.)

248. The applicants sought to overcome Examiner Bradley's October 21, 2015 rejection by invoking the exception of Section 102(b), which provides that:

> (1) DISCLOSURES MADE 1 YEAR OR LESS BEFORE THE EFFECTIVE FILING DATE OF THE CLAIMED INVENTION.—A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if—
>
> (A) the disclosure was made by . . . another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

(DTX-10.1931–932; *see also* Kenesky Tr. 665:2–7

249. To overcome Examiner Bradley's rejection, on November 24, 2015, Par's prosecution counsel, Kenesky, participated in an Applicant-Initiated Interview. (DTX-10.1952; Kenesky Tr. 665:24–66:6.)

250. Prior to the interview, Kenesky sent to Examiner Bradley two unexecuted declarations, purportedly prepared pursuant to 37 C.F.R. § 1.130(a), from named inventor Vinayagam Kannan and from Michelle Bonomi-Huvala, Senior Vice President of Regulatory Affairs at Par Pharmaceutical. (Kenesky Tr.

666:10–15.) Kenesky represented that the unexecuted declarations were designed to "explain how the FDA obtained the subject matter of the [April 2014 Vasostrict® Label] from the inventors." (DTX-10.1955–960; Kenesky Tr. 666:25–67:15.)

251. Paragraph 6 of Kannan's draft declaration stated that "[Kannan] jointly invented the subject matter of the currently-pending claims of the '877 Application with Matthew Kenney." (DTX-10.1957.) Paragraph 6 further stated that "[a]s part of [his] responsibilities, [Kannan] forwarded the details of the joint invention to the regulatory team at PAR STERILE." (DTX-10.1957.)

252. Paragraph 7 of Kannan's draft declaration recited the subject matter of the April 2014 Vasostrict® Label that had been relied upon by Examiner Bradley in her October 21, 2015 Office Action as follows:

> The Label discloses part of the subject matter of the claims, including a method of increasing blood pressure in a hypotensive human. The Label recites that, "[v]asostrict is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive . . . ." *Label*, page 1 (parentheticals omitted). The Label further recites a pharmaceutical composition for intravenous administration having 20 units of vasopressin per mL . . . ." *Label*, page 3. The Label further recites that the vasopressin formulation comprises "chlorobutanol [and] Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6." *Label*, page 6. The Label recites the infusion rate of the claim by stating that "[f]or post-cardiotomy shock start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute." *Label*, page 3.

(DTX-10.1957.) With regard to this subject matter, Mr. Kannan represented that "[t]he FDA obtained this information from me and the other joint inventors." *Id.*

253. The draft declaration by Kannan did not include any statement regarding refrigeration of the diluted vasopressin for up to 24 hours. (DTX-10.1956–58.)

254. During the November 24, 2015 Interview, Examiner Bradley recommended including "an unequivocal statement" in the Kannan declaration that the inventors invented "all of the subject matter" relied upon in the rejection:

> The Examiner stated that the declaration by Inventor Vinayagam Kannan clearly provides a reasonable explanation of how the subject matter in the reference was transferred by the Inventors to the FDA, thus explaining the presence of the FDA as an author of the reference. The Examiner recommended amending paragraph 7 to include a reference to all of the subject matter from the FDA reference relied upon in the rejection and an unequivocal statement that one or more joint inventors invented all of the subject matter relied upon, if possible.

(DTX-10.1954.)

255. In response, Kenesky, as the applicants' representative and prosecution counsel, "asserted that the inventor is responsible for all of the subject matter in the FDA reference and would be able to make this statement." (DTX-10.1954; Kenesky Tr. 666:25–67:9.)

256. On November 24, 2015, Kenesky submitted a Response to the October 21, 2015 Office Action along with an executed declaration from Inventor Kannan. (DTX-10.1927–38.)

257. Compared to the draft declaration, the executed declaration by Inventor Kannan included an additional sentence on Paragraph 6, namely: "Matthew Kenney

and I invented the subject matter of the Label that is cited in the Office Action." (*Compare* DTX-10.1937 *with* DTX-10.1957.)

258. Compared to the draft declaration, the executed declaration by Inventor Kannan included amended language on Paragraph 7 to specify that the named inventors Kannan and Kenney "invented this subject matter." (*Compare* DTX-10.1937 *with* DTX-10.1957; *see also* Kenesky Tr. 667:16–22.) Specifically, the revised paragraph 7 of the Kannan declaration as submitted stated as follows:

> The Label discloses part of the subject matter of the claims, including a method of increasing blood pressure in a hypotensive human. The Label recites that, "[v]asostrict is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive . . . ." *Label*, page 1 (parentheticals omitted). The Label further recites a pharmaceutical composition for intravenous administration having 20 units of vasopressin per mL . . . ." *Label*, page 3. The Label further recites that the vasopressin formulation comprises "chlorobutanol [and] Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6." *Label*, page 6. The Label recites the infusion rate of the claim by stating that "[f]or post-cardiotomy shock start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute." *Label*, page 3. The Label recites refrigeration of the diluted vasopressin for up to 24 hours. *Label*, page 1. The FDA obtained this information from me and Matthew Kenney, ***as we invented this subject matter***.

(DTX-10.1937) (emphasis added). Further, unlike the draft declaration, the executed declaration included an additional statement that "[t]he Label recites refrigeration of the diluted vasopressin for up to 24 hours." (*Compare* DTX-10.1937 *with* DTX-10.1957.)

259. In the accompanying Response, Kenesky represented that the executed declaration by Inventor Kannan "describe[s] that the disclosure of the [April 2014 Vasostrict® Label] was obtained from the inventors of the present application." (DTX-10.1931.) Kenesky further asserted that the April 2014 Vasostrict® Label "is not prior art under 35 U.S.C. § 102(a)(1)" because "[t]he FDA obtained the subject matter of the Label from the regulatory team at PAR STERILE, who received the subject matter from the inventors of the present application." (DTX-10.1934.) Kenesky further requested "withdrawal of the rejection because the claims have not been rejected over any eligible prior art." (DTX-10.1934.)

260. On January 11, 2016, in light of the representations made in the November 24, 2015 Response and accompanying Inventor Kannan declaration, Examiner Bradley withdrew the final rejection of the pending claims over the April 2014 Vasostrict® Label. (DTX-10.1967–68; *see also* Kenesky Tr. 668:1–69:9.) Based on the statements made by Kenesky and in the Kannan declaration, the Examiner concluded that they are "sufficient to overcome the rejection of claims 16-29 based upon [the April 2014 Vasostrict Label]." (DTX-10.1967; *see also* Kenesky Tr. 668:1–69:9.) In doing so, Examiner Bradley noted that "[t]he declaration by Inventor Vanayagam [*sic*] Kannan includes an unequivocal statement that he and Matthew Kenney invented the subject matter disclosed in the FDA Label and relied upon in the rejection (¶6–7). …" (DTX-10.1967; Kenesky Tr. 668:12–20.)

2. Inventor Kannan's Declaration Disqualifying the April 2014 Vasostrict® Label as Prior Art Was False

261. The Kannan declaration (*see* FF 256) is false because the subject matter of the April 2014 Vasostrict® Label relied upon by Examiner Bradley in her October 21, 2015 Office Action was not invented by either or both of Vinayagam Kannan and Matthew Kenney. (*See* FF 262–265.)

262. Matthew Kenney testified that he did not invent or contribute to *any* of the subject matter of the April 2014 Vasostrict® Label:

> **Q**. Now that you have reviewed the label, can you please let me know if you worked on or contributed to any portions of this label, including any content thereof?
>
> **A**. I don't recall doing any work that contributed to the information on this label.

(Kenney Tr. 547:6–11.)

263. Kannan admitted that he did not invent the subject matter of the 2014 Vasostrict Label on which the Examiner relied upon. For instance, Kannan did not invent a method to increase blood pressure in adults with vasodilatory shock who remain hypotensive:

> **Q**. You did not invent the method to increase blood pressure in adults with vasodilatory shock who remain hypotensive as described in the label, correct?
>
> **A**. That is correct, I did not invent.
>
> (Kannan Tr. 530:22–25.)
>
> Kannan also did not invent the vasopressin formulation described in the Label, including a formulation with a pH of 3.4–3.6:

> **Q.** And your declaration goes on to state, "The label further recites that the Vasopressin formulation comprises chlorobutanol and water for injection, USP adjusted with acetic acid to pH 3.4 to 3.6." Do you see that?
>
> **A.** I see that.
>
> **Q.** And that is part of the formulation described in the label, Exhibit 32, that you did not invent, correct?
>
> **A.** Correct.

(Kannan Tr. 531:15–24.)

264. Kannan further did not invent the rate of administration of the vasopressin formulation:

> **Q.** The paragraph 7 of your declaration, Exhibit 34[] goes on to state, "The label recites the infusion rate of the claim by stating that for post cardiotomy shock, start with a dose of 0.03 units per ml -- per minute," excuse me, ["]for septic shock, start with a dose of 0.01 units per minute.["] Do you see that?
>
> **A.** I see that.
>
> **Q.** And you didn't invent that subject matter either, correct?
>
> **A.** Correct.

(Kannan Tr. 531:25–32:10.)

265. The only aspect of the Label that Kannan "may have contributed to" is that the diluted vasopressin may be refrigerated for up to 24 hours. (Kannan Tr. 532:11–16, 534:6–11 ("**Q.** So it's your testimony today, sir, that of all the information that is provided in paragraph 7 of your declaration, you contributed in

some way only to the claim for refrigeration of diluted Vasopressin for up to 24 hours, right? **A.** That is correct.").)

266. At trial, Kannan testified for the first time that he understood the "subject matter," as referenced in Paragraph 7 of his declaration, as "referring to refrigeration of diluted [V]asopressin for up to 24 hours as a combination of all of the items stated in paragraph 7." (Kannan Tr. 718:5–9.)

267. Kannan did not inform the patent office that his only contribution to the subject matter of the 2014 Vasostrict Label related to refrigerated storage of diluted vasopressin. (Kannan Tr. 536:23–37:3) (**Q.** And did you ever correct your declaration to specify that you, as you say now, only meant that you invented the subject matter of the refrigeration conditions? **A.** I don't remember any further communication happened after that.)

268. In reviewing the October 21, 2015 rejection by the Examiner, (DTX-10.1874), Kenesky understood that the "subject matter" the Examiner Bradley was relying upon for her rejection is the same subject matter identified on DTX-10.1874, (which has the bates-number of PAR-VASO-0008326.) (*See* FF 247; Kenesky Tr. 663:3–11.) Kenesky did not inform the patent office that Kannan's only contribution to the subject matter of the 2014 Vasostrict Label related to refrigerated storage of diluted vasopressin. (Kenesky Tr. 665:19–23) ("**Q.** You did not tell the Patent Office during prosecution of the '239 Patent that Mr. Kannan's only

contribution to the subject matter of the FDA label was with respect to refrigeration, did you? **A.** I do not recall such a statement.")

269. Kannan understood that his declaration was submitted for the purpose of overcoming Examiner Bradley's rejection based on the 2014 Vasostrict Label. (Kannan Tr. 738:12–16) (**Court:** "So you knew -- was paragraph 7 submitted, as far as you understand, to overcome the Patent Examiner's concern about the label being prior art that would invalidate the patent? **A.** Yes, Your Honor.")

3. The false inventorship declaration was material

270. Examiner Bradley rejected all pending claims of the '239 Patent as both anticipated and obvious over the April 2014 Vasostrict® Label (DTX-10.1871–77), prior to the withdrawal of the rejection due to disqualification of the April 2014 Vasostrict Label as prior art. (DTX-10.1967–68.)

271. Claim 1 of the '239 Patent, as issued, recites:

> 1. A method of increasing blood pressure in a human in need thereof, the method comprising:
>
> a) providing a pharmaceutical composition for intravenous administration consisting of, in a unit dosage form: i) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof; ii) optionally chlorobutanol; iii) acetic acid, acetate, or a combination thereof; iv) 0-2% vasopressin degradation products; and v) water;
>
> b) diluting the unit dosage form in a diluent to provide a concentration from about 0.1 units/mL to about 1 unit/mL of vasopressin or the pharmaceutically-acceptable salt thereof; and

> c) administering the diluted unit dosage form to the human by intravenous administration;
>
> wherein:
>
> the unit dosage form has a pH of 3.5 to 4.1;
>
> the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and
>
> the human is hypotensive.

(DTX-605.33.)

272. No limitation on refrigerated storage of diluted vasopressin for up to 24 hours is found in the issued claims of the ’239 Patent. (DTX-605.33–34.)

273. Dr. Cross testified that the April 2014 Label for Vasostrict teaches every clinical element of the claims of the ’239 Patent. Specifically, Dr. Cross testified that the April 2014 Label for Vasostrict taught (1) a method to increase blood pressure in patients who are hypotensive; (2) diluting the unit dosage form in a diluent to provide a concentration from about 0.1 units/mL to about 1 units/mL; and (3) administering to patients using dosage of about 0.01 units to 0.1 units of vasopressin per minute. (Cross Tr. 501:9–02:5.)

274. Dr. Park testified that the April 2014 Label for Vasostrict teaches all of the remaining (*i.e.*, nonclinical) claim elements of the ’239 Patent. (Park Tr. 434:24–35:13, 442:14–43:7, 443:19–23.) Specifically, Dr. Park testified that the April 2014 Label for Vasostrict taught the claimed vasopressin formulation with an overlapping

pH of 3.4 to 3.6. (Park Tr. 434:24–35:13.) Dr. Park further testified that Examiner found the claim limitation regarding "0-2% vasopressin degradation products" to be an inherent feature of the prior art Vasostrict formulation. (Park Tr. 442:14–43:7, 443:19–23.)

275. Dr. Park further testified that Lot No. 310571 of the Original Vasostrict product met the claim limitation regarding "0-2% vasopressin degradation products." (Park Tr. 442:21–43:7.) Lot No. 310571 of Original Vasostrict also had a pH of 3.5, which fell within the pH range of 3.5–4.1, as specified in the issued claims of the '239 Patent. (DTX45.6–7, DTX-605.33–34.)

276. Because the 2014 Vasostrict taught every element of the claims, including all of the clinical elements, (FF 84–86, 136; Cross Tr. 501:9–02:5; DDX2-7) and formulation elements, (FF 152; Park Tr. 397:20–98:6), the Examiner would not have issued the '239 Patent but-for the demonstrably false statements by Kenesky and Kannan to disqualify the 2014 Vasostrict Label as prior art. (*See* Chyall Tr. 611:11–19.)

277. After the 2014 Vasostrict Label was disqualified as prior art, the applicants amended the claims to recite a pH range of 3.5–4.1. (DTX-10.2335.)

B. Inequitable Conduct Through Submission Of The False Normalization Declarations During Prosecution of the ’478 and ’239 Patents

278. The ’239 Patent claims priority to U.S. Application No. 14/610,499 (the “’499 Application”), filed January 30, 2015. (DTX-605.2.) The application that issued as the ’239 Patent was filed at the PTO on May 20, 2015, as U.S. Application No. 14/717,877 (the “’877 Application”). (DTX-605.2.) The ’877 Application is a continuation of the ’499 Application and shares a specification with the ’499 Application. (DTX-605.2.)

1. Relying On Normalization to Assert Criticality

279. On October 22, 2015, during prosecution of the application for US Patent No. 9,375,478—a sister application of the ’239 Patent—Examiner Bradley rejected the pending claims as obvious in light of the label for a prior art vasopressin product sold by Pharmaceutical Partners of Canada (PPC), in view of other literature references regarding the clinical uses of vasopressin. (DTX-7.1821, 1828–33.)

280. PPC taught a vasopressin formulation with a pH range of 2.5–4.5. (DTX-7.1830.)

281. On January 22, 2016, in response to Examiner Bradley’s obviousness rejection, the applicants submitted data from the pH stability studies that measured the levels of impurities and the amount of vasopressin left in the formulation (assay), after four weeks storage at 25° C and 40° C. (DTX-7.1883–96.) The first study,

conducted in March 2015, tested vasopressin formulations with a 10 mM acetate buffer, adjusted to pHs 3.5–4.5 (in 0.1 pH unit increments), which were stored for 4 weeks at 25°C and 40°C. (DTX-82.39; DTX-7.1883–96; Chyall Tr. 592:17–93:1.) The second study, conducted in November 2015, tested vasopressin formulations with a 10 mM acetate buffer, adjusted to pHs 2.5 and 3.4. (DTX-82.87; DTX-7.1883–96; Chyall Tr. 593:2–93:23.)

282. The applications used the same lot of vasopressin for the March 2015 study and the November 2015 study. (DTX-82.39, 87; Chyall Tr. 592:12–93:12.) By the time the second study was conducted, vasopressin used to create the formulations for the November 2015 study had degraded. (DTX-82.39, 87; Chyall Tr. 592:12–95:9.) As such, the levels of starting impurities in the formulations used for the November 2015 study were higher than the formulations used for the March 2015 study. (DTX-7.1893–96; Chyall Tr. 594:3–95:2.)

283. Specifically, the first pH stability study (which examined samples from pH 3.5 to 4.5, within the claimed range) used Vasopressin API from lot 19056 that had a purity of 480 units/mL and expired on October 21, 2015. (DTX-82.39; Chyall Tr. 592:17–93:1.)

284. The second pH stability study (which examined samples from pH 2.5 to 3.4, outside the claimed range) used the same Vasopressin API lot 19056 that had

a purity of 456 units/mL, but with an extended expiration date of December 31, 2016 based on a "supplier retest." (DTX-82.87; Chyall Tr. 593:2–93:23.)

285. On January 22, 2016, named inventor Sunil Vandse submitted a declaration (referred to by the Examiner as "Vandse II"), presenting plots of the assay and impurities data generated at each temperature based on the March 2015 and November 2015 studies. (DTX-7.1883–96.)

286. In Figures 1 and 2, Vandse presented the total % impurities present in the formulation after storage for four weeks at 25° C and 40° C, respectively. (DTX-7.1885, 1887–88.) The data presented in these figures were not normalized, as the data did not subtract the levels of starting impurities from the presented values of total % impurities. (Kannan Tr. 540:7–14, DTX-7.1893–96; *see also* Kannan Tr. 722:21–23.)

287. In Figures 3 and 4, Vandse presented the ***% decrease in assay*** after storage for four weeks at 25° C and 40° C. (DTX-7.1885, 1889–90.) The data presented in these figures were normalized, as the % decrease in assay presented in these figures subtracted the starting amounts of vasopressin from the presented assay values. (DTX-7.1885, 1889–90; Kannan Tr. 539:16–40:6.)

288. Based on the data presented in Figures 1–4, the applicants argued that the claimed pH of 3.8 is critical to stability. (DTX-7.1885–86.)

289. On February 2, 2016, in a subsequent Office Action, Examiner Bradley maintained her rejection and noted that both the impurities and assay plots presented in Vandse II declaration included a "break in the data" between pH 3.4 and pH 3.5. (DTX-7.2120, 2130–31; *see also* Chyall Tr. 601:14–1.) The examiner noted that the break "may possibly be attributed to differences between the two experimental batches" of the March 2015 and November 2015 studies. (DTX-7.2130–31; *see also* Chyall Tr. 601:14–1.)

290. On March 11, 2016, during a subsequent interview, "[t]he Examiner reiterated questions raised in the previous Office action regarding the declaration filed 1/22/2016[,]" referring to Vandse II declaration. (DTX-7.2140.) "Specifically, the Examiner asked for Applicant to account for what appears to be a break in the data between pH 3.4 and 3.5 and whether or not this break could be attributed to the fact that the data above and below 3.4 and 3.5 were collected on different days." (DTX-7.2140.)

291. The Examiner also "asked whether the results in Figures 1–4 have been reproduced and stated that ideally the entire range would be evaluated on the same day with the same batch of sample to remove any variability attributable to the different samples." (DTX-7.2140.) "The Examiner stated that more evidence and explanation regarding this data is needed to fully reconsider the rejection." (DTX-7.2140.)

292. Following the interview, the applicants submitted a declaration from Kannan, dated March 31, 2016. (DTX-7.2159–69.) The March 31, 2016 Kannan Declaration stated Kannan "reviewed the Non-Final Office Action of February 2, 2016" and that he "under[stood] the nature of the rejections therein." (DTX-7.2159.)

293. Kannan also acknowledged the Examiner's request for information regarding "what appears to be a break in the data between pH 3.4 and 3.5 and whether or not this break could be attributed to the fact that the data above and below 3.4 and 3.5 were collected on different days." (DTX-7.2163–64.)

294. In the March 31, 2016 Kannan Declaration, Kannan explained "[n]ormalization is a standard technique used by analytical chemists that allows direct comparison between two data sets by removing systematic differences due to, for example, starting amounts of the sample." (DTX-7.2163.) He noted that "normalization simply allows the comparison of results between two data sets." (DTX-7.2163; *see also* Kannan Tr. 537:25–38:11.) He further explained that "the difference in starting amounts between the Vasopressin pH 2.5 to 3.4 Formulations and the Vasopressin pH 3.5–4.5 Formulations was accounted for by normalization of the data." (DTX-7.2163.)

295. In response to the Examiner's request for information regarding "what appears to be a break in the data between pH 3.4 and 3.5 and whether or not this break could be attributed to the fact that the data above and below 3.4 and 3.5 were

collected on different days," Kannan stated that the results "are attributable to pH, and not to the fact that the data were collected on different days." (DTX-7.2163–64.) Kannan stated "because the procedures for each of the experiments were the same, and because pH was the only variable that was not normalized, I conclude that the differences in the assay (% label claim; vasopressin remaining) and % total impurities results for each formulation were attributable to changes in pH." (DTX-7.2163.) Kannan further noted that he is "not aware of any other factors that would account for the differences in the results for each formulation." (DTX-7.2163.)

296. Upon receipt of the March 31, 2016 Kannan Declaration, Examiner Bradley allowed the claims of the '478 Patent without further rejection. (DTX-7.2173.)

297. Subsequently, on November 22, 2016, in prosecution of the '239 Patent application, Examiner Bradley again rejected the claims as obvious over the PPC label (pH 2.5–4.5), along with other literature. (DTX-10.2283, 2285–97.)

298. In response, the applicants again relied on the March 2015 and November 2015 studies, and submitted another declaration from Kannan, dated May 22, 2017. (DTX-10.2334, 2352–72.) Paragraph 31 of the May 22, 2017 declaration again claimed that "[n]ormalization is a standard technique used by analytical chemists that allows direct comparison between two data sets by removing systematic differences due to, for example, starting amount of the sample." (DTX-

10.2369.) In Paragraph 32, the May 22, 2017 declaration also repeated that "pH was the only variable not normalized," that "the differences in the assay (% label claim; vasopressin remaining) and % total impurities results for each formulation were attributable to changes in pH," and that he was "not aware of any other factors that would account for the differences in the results for each formulation." (DTX-10.2369.)

299. After receipt of this declaration, Examiner Bradley granted the claims of the '239 Patent without further rejection. (DTX-10.2817.) In the examiner's statement of reasons for allowance, Examiner Bradley noted that "[t]he declaration under 37 CFR 1.132 filed May 22, 2017 is sufficient to overcome an obviousness rejection over Pharmaceutical Partners of Canada because it establishes the criticality of the claimed pH range of 3.5 to 4.1." (DTX-10.2847.)

2. The normalization declarations were false

300. Although Kannan expressly represented to the USPTO that "pH was the only variable that was not normalized," (DTX-10.2369), this statement was false because Kannan did not submit normalized impurities data. (*See* DTX-10.2369; Kannan Tr. 540:7-14 ("**Q.** . . . [Y]ou didn't normalize [the impurities] in the information provided to the Patent Office, right? **A.** Yes. My understanding is that we did not normalize impurities.") Instead, Kannan reported total impurities of each

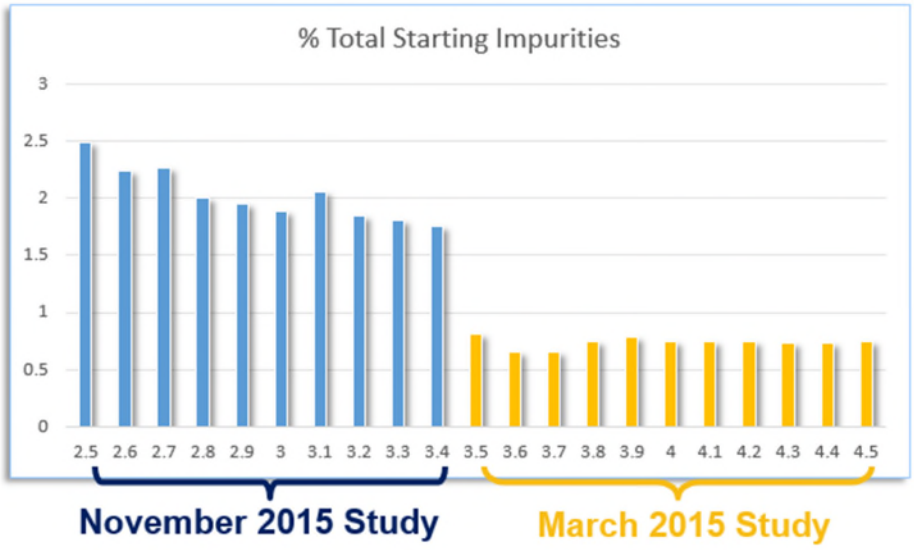
formulation as it existed after the 4-week studies, rather than normalized impurities. (*See* Kannan Tr. 542:6–10; Chyall Tr. 576:7–23, 598:23–99:4; DTX-10.2362–63.).)

301. On March 22, 2016, just nine days before providing his initial declaration, Kannan circulated an e-mail to inventor Kenney that contained normalized impurities graphs and asked whether the graphs "make sense," and stated "[i]f yes, we can clean up and send to Gina." (*Compare* DTX-66.1 (e-mail sent 3/22/2016) *with* DTX-7.2169 (declaration submitted 3/31/2016).) Thus, Kannan knew that pH was not "the only variable that was not normalized" in the graphs submitted to the PTO, and that impurities had not been normalized as well. (*See* DTX-66.1.)

302. Kannan also understood that one purpose of his normalization declarations was to respond to Examiner Bradley's inquiry regarding the effect of using results of two different studies—namely, the March 2015 Study and November 2015 study. (Kannan Tr. 738:17–25 ("The Court: All right. Then look at paragraph 32 of DTX-1073. And what was your understanding of why paragraph 32 had to be presented to the Patent Examiner? **A.** The Patent Examiner had concern that the data came from two different experiments. Wanted to know the effect that we see on that impurity. Was it truly significant or whether it is due to the fact that the experiments, these were two separate experiments. That was the purpose of the paragraph to explain to the Examiner.").)

3. The normalization declarations were material

303. Reporting total impurities, rather than the relative impurities that formed over the 4-week study period, skewed the results that were presented to the Patent Office. (Chyall Tr. 594:3–95:9.) The levels of starting impurities for the November 2015 study were higher than the levels of stating impurities for the March 2015 study, which included the claimed pH range, as illustrated in the demonstrative created by Dr. Chyall.



(Chyall Tr. 594:3–95:9, 599:5–01:3)

304. Kannan admitted that the impurities for the high pH formulations had not even reached the starting levels of the low pH formulations by the end of the four-week study. Specifically, he testified as follows:

> **Q.** So if we look at the starting total impurities at 3.4, there were 1.75 percent at initial?
>
> **A.** Correct.

Q. And at 3.5, 0.815 percent, correct?

A. Correct[.]

Q. And so the 3.4[] 25 degree sample started with more than twice the amount of impurities as the 3.5 sample, correct?

A. Mathematically, yes.

Q. And at four weeks, the 3.5 sample hadn't even reached the starting impurities [point] for the 3.4 sample, correct?

A. At 3.4 weeks at 25 C, it is 2.03 percent. And at pH 3.5, it is 1.23 percent.

(Kannan Tr. 543:18–44:6.)

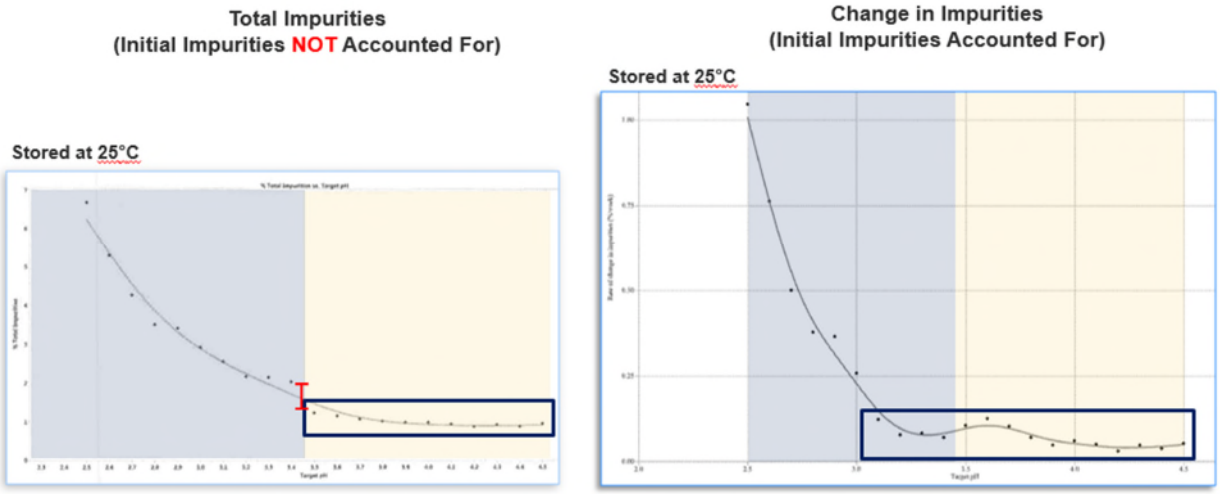
305. Kannan understood that the break in the data between pH 3.5 and pH 3.4 could be due to significant differences in the levels of starting impurities between the high pH and low pH formulations used in the two studies. (Kannan Tr. 544:7–12 ("**Q.** Right. And so it's the difference in the starting point of impurities that accounts for the break between the data in the total impurities at 25 degree C between 3.4 and 3.5 pH, correct? **A.** It may be possible that that could be the difference.").)

306. Kannan testified at trial that the Examiner had all of the raw data that was underlying the graphs presented in his declaration. (Kannan Tr. 723:10–14). But Dr. Chyall testified that in order to have generated a normalized impurities graph, assuming that she appreciated that Dr. Kannan's normalization representation was false, Examiner Bradley would have had to "find the raw data" and perform the "subtraction of the impurities in order to get the change in impurity." (Chyall Tr.

603:17–04:4.) Thereafter, Examiner Bradley "would have had to have taken that data and then make her own chart of the normalized impurity and then compare that chart to the chart that was provided in a declaration." (*Id.*)

307. Because of the differences in starting assay and starting total impurities, in order to rely on results of the two studies, it was important that Par normalize the results for both variables, rather than just assay. (Chyall Tr. 594:3–96:11.)

308. At least the graph of normalized impurities after storage at 25° C undermines the statements in Kannan's declaration that a pH of 3.8 ('478 Patent) or 3.5–4.1 ('239 Patent) is critical. (Chyall Tr. 599:5–01:3.) Rather than showing a relatively large gap between the total impurities at pH 3.4 and 3.5, the normalized graph showed that impurities were comparable across the range of pH 3.1 to 4.5. (*Compare* DTX-10.2362 *with* DTX-67; DDX4-22; Chyall Tr. 599:5–01:3)



309. Because PPC taught nearly every element of the claims, including a pH that encompassed the claimed range, and only granted the claims on the basis of Dr.

Kannan's criticality showing, the Examiner would not have issued the '239 Patent but-for the fact that Kenesky and Kannan withheld normalized impurity data from the Examiner, which demonstrated a broader pH range for stable vasopressin formulations. (*See* Chyall Tr. 591:2–7) (noting the graphs do not establish criticality over the prior art range).

C. The Inequitable Conduct During Prosecution of the '478 and '239 Patents Infected the Asserted Patents.

310. Examiner Bradley, who prosecuted the '239 Patent, also prosecuted the Asserted Patents. (JTX-2 at Cover; JTX-3 at Cover.)

311. The named inventors of the '478 Patent are the same as those of the Asserted Patents. (JTX-2 at Cover; JTX-3 at Cover; DTX-7.1873–76.) The named inventors of the '239 Patent—Matthew Kenney and Vinayagam Kannan—are also named inventors of the Asserted Patents. (JTX-2 at Cover; JTX-3 at Cover; DTX-605.2.)

312. After the applicants disqualified the April 2014 Vasostrict Label as prior art during prosecution of the '239 Patent, the Examiner did not identify the Label as prior art for any subsequent prosecution of any application in the '239 Patent family. (*See, e.g.*, JTX-8 at PAR-VASO-0005732–34; JTX-9 at PAR-VASO-0009649–50.) Instead, the Examiner cited the 2014 Vasostrict during prosecution of the Asserted Patents only as an "evidentiary reference [that] does not need to be prior art" to show conversion of units of vasopressin to milligrams. (*Id*.)

313. The April 2014 Vasostrict Label taught all of the clinical elements of claim 1 of the ’209 Patent. (Cross Tr. 501:9–02:5.)

314. The April 2014 Vasostrict Label taught all of the remaining (*i.e.*, nonclinical) claim elements of the Asserted Patents, except for the pH limitation, for which the Label disclosed an abutting pH of 3.4 to 3.6, compared to the claimed pH of 3.7–3.9 of the Asserted Patents. (Park Tr. 444:6–45:7.) Specifically, Dr. Park testified that the April 2014 Label for Vasostrict taught the claimed vasopressin formulation with an abutting pH of 3.4 to 3.6. (Park Tr. 444:6–45:7.) Dr. Park further testified that Lot No. 310571 of the Original Vasostrict product met the claim limitation regarding the amount of impurities. (Tr. 444:17–25.)

315. Had the April 2014 Label for Vasostrict not been disqualified as prior art during prosecution of the ’239 Patent, the March 2015 and November 2015 studies submitted by the inventors and incorporated into Examples 9 and 10 of the ’209 and ’785 Patents could not have established criticality of Original Vasostrict, described in the April 2014 Label. (Chyall Tr. 611:13–12:4.) Specifically, while the March 2015 and November 2015 studies are four-week laboratory studies that tested the pH range 2.5–4.5, (DTX-7.1883–96; DTX-82.39, 87), the FDA-approved Original Vasostrict has a narrower pH range of 3.4–3.6, with stability established by months of FDA-submitted stability data. (Chyall Tr. 611:13–12:4.)

316. Therefore, the Asserted Patents would not have issued had the 2014 Vasostrict Label been considered prior art by the Examiner.

317. Although Par did not resubmit the Kannan II declaration during prosecution of the Asserted Patents, Par instead incorporated that data into Examples 9 and 10 of the specification for each Asserted Patent and identified those Examples in arguing patentability. (Chyall Tr. 775:16–23; JTX-2 at 97:40–99:15; JTX-3 at 96:40–98:37.)

318. Further, the applicants relied on the same set of pH stability data generated from the March 2015 and November 2015 studies in prosecution of the Asserted Patents to demonstrate criticality of the claimed pH of 3.7–3.9 over PPC. (JTX-8 at PAR-VASO-0005732–34, PAR-VASO-0005816–17, PAR-VASO-0006436; JTX-9 at PAR-VASO-0009649–50, PAR-VASO-0009721–22, PAR-VASO-0010349.) Kannan's misrepresentation regarding normalization of the impurities data rendered the Examiner unable to make an accurate determination regarding the criticality of the claimed pH. (*See* Chyall Tr. 601:14–1, 603:5–10.)

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Respectfully submitted,

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